GP/1644

PATENT

Attorney Docket No. UM-06340

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Peter A. Ward *et al.*
Serial No.: 09/878,603 Group No.:1644
Filed: 10/12/01 Examiner: A. Decloux
Entitled: **Compositions And Methods For The Treatment Of Sepsis**

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: November 12, 2002 By: Traci E. Light

Sir or Madam:

The citations listed below, copies attached, may be material to the examination of the above-identified continuation application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are referred to in the body of the specification:

11/10/2002 SZEWDIE1 00000075 09878603
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- U.S. Pat. No. 4,357,272 to Polson;
- U.S. Pat. No. 5,904,922 to Carroll;
- U.S. Pat. No. 5,585,089 to Queen *et al.*;
- U.S. Pat. No. 5,565,332 to Hoogenboom *et al.*;
- U.S. Pat. No. 5,658,727 to Barbas *et al.*;
- U.S. Pat. No. 5,260,203 to Ladner *et al.*;
- U.S. Pat. No. 5,192,746 to Lobl, *et al.*;
- U.S. Pat. No. 5,169,862 to Burke, Jr., *et al.*;

- U.S. Pat. No. 5,539,085 to Bischoff, *et al.*;
- U.S. Pat. No. 5,576,423 to Aversa *et al.*;
- U.S. Pat. No. 5,051,448 to Shashoua;
- U.S. Pat. No. 5,559,103 to Gaeta *et al.*;
- EP 025949;
- Machiedo *et al.*, "Patterns Of Mortality In a Surgical Inventive Care Unit," *Surg. Gyn. & Obstet.*, 152: 757-759 (1981);
- Morris *et al.*, "Endotoxemia in neonatal calves given antiserum to a mutant *Escherichia coli* (J-5)," *Am. J. Vet. Res.*, 47: 2554-2565 (1986);
- Hoffman *et al.*, "Prognostic Variables for Survival of Neonatal Foals Under Intensive Care," *J. Vet. Int. Med.*, 6: 89-95 (1992);
- S.M. Wolff, "Monoclonal Antibodies And The Treatment Of Gram-Negative Bacteremia And Shock," *New Eng. J. Med.*, 324: 486-488 (1991);
- Schulman *et al.*, "Cost-effectiveness of HA-1A Monoclonal Antibody for Gram-Negative Sepsis," *JAMA*, 266: 3466-3471 (1991);
- Mandecki *et al.*, "Chemical Synthesis of a gene encoding the human complement fragment C5a and its expression of *Escherichia coli*," *Proc. Natl. Acad. Sci. U S A*, 82(11): 3543- 7 (1985);
- Koehl, J. and Bitter-Suermann, D., *Anaphylatoxins. Complement in health and disease.*, Edited by Whaley, K., Loos, M., Weiler, J.M., Kluwer Academic publishers, pp 299-324, (1993);
- Van Epps *et al.*, "Relationship of C5a Receptor Modulation to the Functional Responsiveness of Human Polymorphonuclear Leukocytes of $C5a^{1}$," *J. Immunol.*, 150: 246-252 (1993);
- Ward, P.A. and Becker, E.L., "The Deactivation of Rabbit Neutrophils by Chemotactic Factor and the Nature of the Activatable Esterase," *J. Exp. Med.*, 127: 693-709 (1968);
- Solomkin *et al.*, "Neutrophil dysfunction in sepsis. II. Evidence for the role of complement activation products in cellular deactivation," *Surgery*. 90: 319-327 (1981);

- Kohler, G. and Milstein, C., "Continuous cultures of fused cells secreting antibody of predefined specificity," *Nature*, 256: 495 (1975);
- Kennet, R.H., "*Monoclonal Antibodies, Hybridoma--A New Dimension in Biological Analysis*," Plenum Press, NY (1980);
- Kozbor and Roder, "The production of monoclonal antibodies from human lymphocytes," *Immunol. Today*, 4: 72-79 (1983);
- Elzaim *et al.*,"Generation of Neutralizing Antipeptide Antibodies to the Enzymatic Domain of *Pseudomonas aeruginosa* Exotoxin A," *Infect. Immun.*, 66(5):170-9 (1998);
- Kettleborough *et al.*, "Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation," *Protein Engineering*, 4(7): 773-783 (1991);
- Rothermel *et al.*, "Nucleotide and corrected amino acid sequence of the functional recombinant rat anaphylatoxin C5a[1]," *Biochim. Biophys. Acta*, 1351 (1-2), 9-12 (1997);
- Babkina *et al.*, *Bioorg. Khim.*, 21(5): 359-64 (1995)[1];
- Gerard *et al.*, "Amino Acid Sequence of the Anaphylatoxin from the Fifth Component of Porcine Complement," *J. Biol. Chem.* 255(10): 4710-4715 (1980);
- Zarbock *et al.*, "A proton nuclear magnetic resonance study of the conformation of bovine anaphylatoxin C5a in solution," *FEBS Lett.*, 238(2): 289-294 (1988);
- Stryer ed., "Biochemistry," 2nd ed,, WH Freeman and Co.[1981];
- Nilsson *et al.*, "Affinity Fusion Strategies for Detection, Purification, and Immobilization of Recombinant Proteins," *Prot. Expr. Purif.*, 11(1):1-16 (1997);
- Gluzman, "SV40-Transformed Simian Cells Support the Replication of Early SV40 Mutants," *Cell*, 23: 175 (1981);
- Davis *et al.*, "Basic Methods in Molecular Biology," (1986);

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[1] We have been unable to obtain this reference, but if the examiner request a copy we will seek to obtain it.

- Wilson, *et al.*, "The Structure of an Antigenic Determinant in a Protein," *Cell*, 37: 767 (1984);
- Evans *et al.*, "An engineered poliovirus chimaera elicits broadly reactive HIV-1 neutralizing antibodies," *Nature*, 339: 385 (1989);
- Huang *et al.*, "Vaccinia Virus Recombinants Expressing an 11-Kilodalton β-Galactosidase Fusion Protein Incorporate Active β-Galactosidase in Virus Particles," *J. Virol.*, 62: 3855 (1988);
- Schlienger *et al.*, "Human Immunodeficiency Virus Type 1 Major Neutralizing Determinant Exposed on Hepatitis B Surface Antigen Particles Is Highly Immunogenic in Primates," *J. Virol.*, 66:2 (1992);
- Posnett *et al.*, "A Novel Method for Producing Anti-peptide Antibodies," *J. Biol. Chem.*, 263: 1719 (1988);
- Nardelli *et al.*, "A Chemically Defined Synthetic Vaccine Model for HIV-1[1]," *J. Immunol.*, 148:914 (1992);
- *Current Protocols in Molecular Biology*, Eds. Ausabel *et al.*, N.Y.: John Wiley & Sons, (1991)[2];
- Hochuli *et al.*, "New Metal Chelate Adsorbent Selective For Proteins And Peptides Containing Neighbouring Histidine Residues," *J. Chromatography*, 411: 177 (1987);
- *Current Protocols in Molecular Biology*, Eds. Ausubel *et al.*, John Wiley & Sons (1992)[3];
- Caruthers *et al.*, "New chemical methods for synthesizing polynucleotides," *Nuc. Acids Res. Symp. Ser.*, 7: 215-233 (1980);
- Crea and Horn, "Synthesis of oligonucleotides on cellulose by a phosphotriester methods," *Nuc. Acids Res.*, 9: 2331 (1980);
- Matteucci and Caruthers, "The Synthesis of Oligodeoxypyrimidines on a Polymer Support," *Tetrahedron Lett.*, 21: 719 (1980);

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[2] Because this is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

[3] Because this is a general text that was cited in the specification without direction to any specific page, applicants have not included any excerpts with this IDS.

- Chow and Kempe, "Synthesis of oligodeoxyribonucleotides on silica gel support," *Nuc. Acids Res.*, 9: 2807-2817 (1981);
- Creighton, *Proteins Structures And Molecular Principles*, W. H. Freeman & Co., New York, NY (1983);
- Roberge *et al.*, "A Strategy for a Convergent Synthesis of *N*-Linked Glycopeptides on a Solid Support," *Science*, 269: 202-204 (1995);
- R.C. Bone, "The Pathogenesis of Sepsis," *Ann. Intern. Med.*, 115: 457-469 (1991);
- E.S. Caplan and N. Hoyt, "Infection Surveillance and Control in the Severely Traumatized Patient," *Am. J. Med.*, 70: 638-640 (1981);
- Meek *et al.*, "The Baltimore Sepsis Scale: Measurement of Sepsis in Patients with Burns Using a New Scoring System," *J. Burn Care Rehab.*, 12: 564-568 (1991);
- R.L. Nichols, "Classification of Surgical Wounds and Nonoperative Factors Influencing Surgical Wound Infection," *Decision Making in Surgical Sepsis*, B.C. Decker, Inc., Philadelphia, pp. 20-21 (1991);
- Stahel *et al.*, "TNF-α-Mediated Expression of the Receptor for Anaphylatoxin C5a on Neurons in Experimental *Listeria* Meningoencephalitis," *J. Immunol.*, 159(2): 861-9 (1997);
- W.K. Joklik *et al.* (eds.), "Streptococcus pneumoniae," *Zinsser Microbiology*, 18th ed., p. 485, Appleton-Century-Crofts, Norwalk, CT (1984);
- J.M. Slack and I.S. Snyder, *Bacteria and Human Disease,* pp. 128-133, Yearbook Medical Publishers (1978);
- G.P. Youmans *et al.*, *Biologic and Clinical Basis of Infectious Diseases*, 3d ed., p. 553, W.B. Saunders Co., (1985);
- Hill, J.H. and Ward, P.A., "The Phlogistic Role of C3 Leukotactic Fragments in Myocardial Infarcts of RatsI," *J. Exp. Med.*, 133: 885-900 (1971);
- Deitch, E.A., *Schock*, 9: 1-11, (1997)[4];

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[4] We have been unable to obtain this reference, but if the examiner request a copy we will seek to obtain it.

- Mulligan *et al.*, "Requirement and Role of C5a in Actue Lung Inflammatory Injury in Rats," *J. Clin. Invest.*, 98: 503-512 (1996);
- Olson *et al.*,"The Role of C5 in Septic Lung Injury," *Ann. Surg.*, 202: 771-776 (1985);

Applicants have become aware of the following printed publications which may be material to the examination of this application:

- U.S. Pat. No. 5,340,923 to Carroll teaches methods for making and purifying anti-venoms suitable for treatment of humans and animals. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- NCBI Accession Number A57689 discloses the amino acid sequence for the rat complement component C5a peptide. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- NCBI Accession Number P12082 discloses the amino acid sequence for the bovine complement C5a anaphylatoxin. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- NCBI Accession Number P01032 discloses the amino acid sequence for the porcine complement C5a anaphylatoxin. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- Czermak *et al.*, "Protective effects of C5a blockade in sepsis," *Nature Med.*, 5(7): 788-92 (1999) discloses the partial amino acid sequence of the rat C5a peptide (*i.e.* amino acid residues 17-36). The reference does not disclose a

composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

- Zhong *et al.*, "Production, specificity, and functionality of monoclonal antibodies to specific peptide-major histocompatibility complex class II complexes formed by processing of exogenous protein," *Proc. Natl. Acad. Sci. USA*, 94: 13856-13861 (1997) discloses the amino acid sequence of synthetic peptides representing residues 46-61 and 116-129 of hen egg lysozyme. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- Hatherhill *et al.*, "Effects of Anti-C5a Antibodies on Human Polymorphonuclear Leukocyte Function: Chemotaxis, Chemiluminescence, and Lysosomal Enzyme Release," *J. Biol. Response Mod.*, 8(6): 614-624 (1989) discloses the production of murine monoclonal antibodies to the porcine C5a peptide. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- Larrick *et al.*, "Characterization of Murine Monoclonal Antibodies That Recognize Neutralizing Epitopes on Human C5a," *Infect. & Immunity*, 55: 1867-72 (1987) teaches the generation of a panel of murine anti-human C5a peptide antibodies which bind to des-Arg C5a. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- Mohr *et al.*, "Effects of anti-C5a monoclonal antibodies on oxygen use in a porcine model of severe sepsis," *Eur. J. Clin. Invest.*, 28: 227-234 (1998) teach the use of a monoclonal anti-pig C5a antibody which was raised in rabbits against the C-terminal region of pig C5a *in vivo* in pigs injected with *E. coli*. The reference does not disclose a composition comprising an isolated and

purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

- Stevens *et al.,* "Effects of Anti-C5a Antibodies on the Adult Respiratory Distress Syndrome in Septic Primates," *J. Clin. Invest.*, 77: 1812-1816 (1986) teach the generation of anti-human $C5a_{desArg}$ antibodies raised in rabbits against human $C5a_{desArg}$ peptide (*i.e.* the full-length C5a peptide minus the terminal arginine residue), wherein said peptide was prepared from activated human plasma. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- Park *et al.,* "Attenuation of Endothelium-Dependent Dilation of Pig Pulmonary Arterioles After Cardiopulmonary Bypass is Prevented by Monoclonal Antibody to Complement C5a," *Anesth. Analg.*, 89: 42-49 (1999) teach porcine pulmonary endothelial dysfunction associated with cardiopulmonary bypass may be mediated by C5a. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

The references listed below were cited in the corresponding International Search Report:

- Kola *et al.,* "Epitope mapping of a C5a neutralizing mAb using a combined approach of phage display, synthetic peptides and site-directed mutagenesis," *Immunotechnology*, 1: 115-126 (1996) defines the epitope of an anti-hC5a specific mAb that recognizes both hC5a and $hC5a_{desArg}$. In defining this epitope they used a combined approach comprising the techniques of bacteriophage random octapeptide library, synthetic peptides and site-directed mutagenesis. Said techiniques all targeted or involved residues 65-74 of human C5a. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

- Ames *et al.*, "Isolation of Neutralizing Anti-C5a Monoclonal Antibodies from a Filamentous Phage Monovalent Fab Display Library," *J. of Immunology*, 152: 4572-4581 (1994) teach production of a panel of mAbs against activated complement component C5a obtained from iterative selection against a filamentous phage M13-FAb display library generated from mice immunized with human rC5a. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- WO 96/39503 teaches polypeptide analogues derivatives of human C5a that are C5a receptor antagonists which are reported to exhibit no substantially no anaphylatoxin or agonist activity. The reference discloses the entire amino acid sequence of the human C5a peptide but does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.
- EP 0245993 A teaches monoclonal antibodies directed to C5a and methods of using these antibodies and discusses the use of des-Arg C5a peptides as antigens. The reference does not disclose a composition comprising an isolated and purified peptide defined by an amino acid sequence selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: November 12, 2002

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